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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/418,221	10/14/1999	NAGESH K. MAHANTHAPPA	ONV-043.01(1	8622

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EXAMINER
BRANNOCK, MICHAEL T

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 04/17/2002 17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/418,221	Mahanthappa et al.
Examiner	**Art Unit**
Michael Brannock, Ph.D.	1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 7, 2002*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3-5, 18-23, 25-28, and 31* is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3-5, 18-23, 25-28, and 31* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Status of Application: Claims and Amendments

1. Applicant is notified that the amendments put forth in Paper 14, 2/7/02, have been entered in full.

2. Claims 1, 3-5, 18-23, 25-28, and 31 are pending.

Upon further consideration, the finality of the previous office action is withdrawn. It is noted that a Notice of Appeal has been filed. Applicant can request a refund for the associated fees or leave it as credit for future appeals.

Withdrawn Rejections:

3. Applicant is notified that any outstanding rejection that is not expressly maintained in this Office Action, has been withdrawn.

Specification

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reasons: The specification makes reference to specific polynucleotide and/or polypeptide sequences; these references must contain a sequence identifier of the form: SEQ ID NO: X, see pages 7 and 48 for example. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 3-5, 18-23, 25-28, and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As set forth in the previous Office action, the phrase "cerebral infarct volume" as it is used in claim 1 renders the claim indefinite, because it is inconsistent with the preamble recitation of neuronal cells. Put another way, the preamble requires "a method for limiting damage to neuronal cells" yet it is unclear if this goal is specifically accomplished by the remaining steps of the claim, i.e. the preamble requires treatment of any neuronal cell that has been damaged by ischemia or hypoxia but the "effective amount" of the polypeptide is only that which is effective at reducing cerebral cell death. This situation introduces several areas of ambiguity into the claim. For example, it is unclear if Applicant is claiming a method of limiting the damage of only those neuronal cells involved in a cerebral infarct or is Applicant claiming a method for limiting the damage of any neuronal cells that could be damaged by ischemic or hypoxic conditions. Thus, it is unclear whether the claim requires that "an amount effective for reducing cerebral infarct volume" also be effective for reducing other damaged neuronal cell

types - as suggested by the preamble. Such a distinction would clearly effect the metes and bounds of the claim.

In the phrase "an amount effective for reducing infarct volume by at least 50% relative to the absence of administration", the limitation "at least 50% relative to the absence of administration" renders the bounds of the claims unascertainable. While it might be possible for the artisan to determine the degree of reduction in infarct volume in mouse or other animal models, the claims encompass treatment of humans and one highly skilled in the art would not be able to make such a distinction "relative to the absence of administration". It would be impossible for the skilled artisan to know whether or not the amount of administered peptide reduced the infarct volume at least 50% (or 70%) relative to the absence of administration in a particular human patient. The art recognizes the difficulty in extrapolating from animal models of stroke to human patients, wherein accurate morphological assessment of infarct volumes can be made for the former, whereas assessments are usually based on functional outcomes for the latter, see Hsu, CY, Stroke 27(12)2298, 1996. Thus, it would be impossible for the skilled artisan to recognize whether or not he or she was indeed practicing the invention as claimed as it relates to human patients. It is suggested to Applicant that the skilled artisan would reasonably be able to determine an amount effective for reducing cerebral infarct volume in humans.

Further the recitation of the term " hedgehog polypeptide" without reference to a particular amino acid or nucleic acid sequence renders the claims indefinite because the specification has not put forth that material or functional element that is indicative of a

"hedgehog polypeptide" and nor is such a definition known in the prior art which clearly sets forth which polypeptides are hedgehog polypeptides and which are not. Therefore the metes and bounds of the claims cannot be determined.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 3-5, 18-23, 25-28, and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating cerebral ischemia, comprising the administration of a mammalian sonic hedgehog polypeptide of SEQ ID NO: 10 or 14, does not reasonably provide enablement for the treatment, prevention, or protection for other neuropathies, nor for the treatment of any neuropathy comprising the administration of polypeptide other than a mammalian sonic hedgehog polypeptide or an N-terminal auto-proteolytic fragment thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The specification presents the results obtained using a mouse model of stroke, comprising the administration of a mammalian sonic hedgehog, presumably that of the murine SEQ ID NO: 12, although it does not appear that the specification actually teaches which sonic hedgehog

is used. The claims claim methods using any polypeptide that could be termed a "hedgehog" polypeptide, yet the specification has not provided sufficient guidance as to which other polypeptides would work as claimed. Further, as currently worded claim 1 appears to encompass any neuropathy caused by ischemia or hypoxic conditions, yet the specification has failed to teach which neuropathies other than cerebral ischemia are amenable to treatment with an amount of hedgehog polypeptide effective for reducing cerebral infarct volume by 50% - as is required by the claim. One of skill in the art appreciates that the many known hedgehog polypeptides provide for a tremendous and disparate array of developmental controls, determining cell fates in embryonic muscle, lung, and nervous tissues. There is no teaching in the specification as to which of this vast array of proteins, natural or created, could be used in the claimed methods. The prior art is also silent as to which of the proteins, with the exception of sonic hedgehog (see below) could be used to practice the claimed methods. One could only guess at which, if any, could be used; and one of skill in the art would certainly not expect that all could be used. In fact, Engber et al., *Soc. Neurosci. Abs.* 26(1-2)Abs No. 792.14, 2000, report that systemic administration of sonic hedgehog, but not desert hedgehog, improved functional recovery following sciatic nerve crush. Thus, it appears that, in the art of systemic administration of hedgehog for the treatment of neuronal cells, the specificity of the hedgehog polypeptide is critical, e.g. sonic and desert hedgehog are 80% identical, yet sonic hedgehog is effective in the treatment of sciatic nerve crush whereas desert hedgehog is not.

Further, the claims encompass variants of the disclosed sonic hedgehog polypeptides, i.e, the specification contemplates such variants as being encompassed by the term "hedgehog polypeptide" (see page 24 for example), yet the specification has not provided sufficient guidance as to how to make such variants. One of skill in the art is left to extensive experimentation wherein amino acids are randomly changed, deleted, or added to a hedgehog polypeptide, and through trial and error experimentation is left to determine when a polypeptide is obtained that could used to reduce cerebral infarct volume by 50 or 70%. Such extensive random trial and error experimentation is considered undue.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without

undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active variants or portions that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

Due to the large quantity of experimentation necessary to generate the almost limitless number of variants and portions required by the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

10. Claims 1, 3-5, 18-23, 25-28, and 31 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No: 5789543.

U.S. Patent No: 5789543 teaches that ischemia resulting form stroke can be treated with a hedgehog polypeptide, see col 26, line 12. Further, the sonic hedgehog polypeptides taught in the 5789543 patent appear to be the same as those taught in the instant application, absent evidence to the contrary, thus it would be inherent to the practice of the methods of the 5789543 patent that the cerebral infarct volume would be reduced by at least 70% relative to the absence of hedgehog polypeptide administration. Further, the additional treatment methods recited in claims 26-28 are old and established adjunct therapies for stroke, as admitted in the instant specification, e.g. page 9, as also understood by anyone practicing the methods of U.S. Patent No: 5789543. Thus it can be reasonably assumed that one practicing the method of U.S. Patent No: 5789543 would also incorporate the additional methods in the treatment of stroke, absent evidence to the contrary.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

April 10, 2002

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600